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# Detecting Human-to-Human Transmission of Avian Influenza A (H5N1)

**To the Editor:** This letter is in response to a recently published article about statistical modeling to assess human-to-human transmission of avian influenza A (H5N1) viruses in 2 case clusters (1). Sporadic cases and clusters of human infection with highly pathogenic avian influenza A (H5N1) viruses have occurred after direct contact with diseased or dead poultry (2,3). Limited, nonsustained human-to-human transmission of avian influenza (H5N1) viruses is believed to have occurred in some clusters (4). Every human infection with a novel influenza A virus should be investigated, and suspected clusters should be investigated immediately to assess exposures and transmission patterns.

Yang et al. applied a statistical model to evaluate publicly available data from 2 case clusters of human infection with avian influenza A (H5N1) viruses (1). These clusters were investigated in detail during 2006 by field epidemiologic investigation teams. Yang et al. suggest that statistical methods can prove or confirm human-to-human transmission, but this suggestion is misleading. Modeling approaches can suggest transmission modalities to account for case patterns, but determination of human-to-human transmission requires detailed field epidemiologic investigations in which human, animal, and environmental exposures as well as clinical and laboratory data are assessed and interpreted.

Indication that a novel influenza A virus has acquired the ability to spread among humans could be reflected by a change in the epidemiology of clusters, such as increases in 1) size and frequency of clusters, 2) cases among nonrelated persons, and 3) clinically mild cases. This ability could also be reflected in accompanying changes in viruses isolated from case-patients. When facing emerging infectious disease threats such as those posed by highly pathogenic avian influenza A (H5N1) viruses, surveillance should rapidly detect human cases and case clusters and facilitate accurate identification of the agent. Field epidemiologic investigations, initiation of

evidence-based clinical management of case-patients, and epidemiologic disease-control methods (including appropriate infection control measures) should be implemented immediately. Statistical modeling can provide useful and supportive insights but should not be viewed as an alternative to a detailed field epidemiologic investigation combined with laboratory data. Timely and comprehensive field investigations remain most critical to guiding decisions about containment efforts for pandemic influenza and other emerging infectious diseases (5).

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**In response:** We thank Drs Uyeki and Bresee for their thoughtful commentary (1) on our article about assessing the possibility of human-to-human transmission of avian influenza A (H5N1) in observed clusters (2). We agree with them that statistical models are not substitutes for careful epidemiologic investigations combined with laboratory data. We believe that the statistical model that we advance can be an important tool to use in conjunction with sound and rapid epidemiologic investigation and intervention.

We do not claim, however, that our statistical model can prove or confirm human-to-human transmission, as Uyeki and Bresee state. In our article, we were careful to point out that we found statistical evidence of human-to-human transmission ( $p = 0.009$ ) in Sumatra. We did not claim to have proven or confirmed human-to-human transmission on the basis of our statistical analysis. A strict interpretation of what we found is that the data from the cluster in northern Sumatra provided evidence to reject the null hypothesis of no human-to-human transmission. Given this, we then weighed all the epidemiologic and laboratory information available to make a scientific judgment about the likelihood of human-to-human transmission. We are not aware of any logical system analogous to Koch's postulates (3) (i.e., proving the causal link between an infectious agent and clinical disease) for actually proving that an infectious agent is transmitted from person to person. However, we believe that the statistical, epidemiologic, and laboratory evidence combined weigh heavily toward the presence of limited human-to-human transmission in the case of the Sumatra cluster.

This statement can be contrasted with our analysis of the cluster in eastern Turkey, where we did not find statistical evidence of human-to-human transmission of avian influenza A (H5N1). This analysis must be evaluated with the epidemiologic and laboratory data. We simply state that we do not have enough statistical evidence to reject the null hypothesis of no human-to-human spread. Whether human-to-human transmission occurred is a scientific judgment.

We agree with Uyeki and Bresee that statistical modeling can provide useful and supportive insights, and we hope that epidemiologic teams who investigate and control potential

infectious disease outbreaks will carry the TranStat software (2) into the field with them. We are grateful that Uyeki and Bresee point out that immediate implementation of containment measures is critical, even while we sort out the cause of an observed cluster of cases. Actually containing possible spread of a potential pandemic strain of influenza (4,5) is more important than scientific arguments about the transmissibility of the infectious agent in question.

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